SUPPLEMENT ARTICLE

Rotavirus Vaccines: Targeting the Developing World

Roger I. Glass,[1] Joseph S. Bresee,[1] Reina Turcios,[1] Thea K. Fischer,[1] Umesh D. Parashar,[1] and A. Duncan Steele[2]

[1]Viral Gastroenteritis Section, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

For the past 2 decades, rotavirus infection, the most common cause of severe diarrhea in children, has been a priority target for vaccine development. This decision to develop rotavirus vaccines is predicated on the great burden associated with fatal rotavirus disease (i.e., 440,000 deaths/year), the firm scientific basis for developing live oral vaccines, the belief that increased investment in development at this time could speed the introduction of vaccines in developing countries, and the appreciation that implementation of a vaccine program should result in a measurable decrease in the number of hospitalizations and deaths associated with rotavirus disease within 2–3 years. RotaShield (Wyeth-Ayerst), the first rotavirus vaccine licensed in the United States, was withdrawn after 9 months because of a rare association of the vaccine with the development of intussusception. In the developing world, this vaccine could still have had a measurable effect, because the benefits of preventing deaths due to rotavirus disease would have been substantially greater than the rare risk of intussusception. Two live oral vaccines being prepared by GlaxoSmithKline and Merck have completed large-scale clinical trials. The GlaxoSmithKline vaccine has been licensed in Mexico and the Dominican Republic, and the Merck vaccine could be licensed in the United States within 1 year; several other candidate vaccines are in earlier stages of testing. However, many challenges remain before any of these vaccines can be incorporated into childhood immunization programs in the developing world. First, vaccine efficacy, which has already been demonstrated in children in industrialized and middle-income countries, needs to be proven in poor developing countries in Africa and Asia. The safety of vaccines with regard to the associated risk of intussusception must be demonstrated as well. Novel financing strategies will be needed to ensure that new vaccines are affordable and available in the developing world. Decision makers and parents in developing countries need to know about this disease that has little name recognition and is rarely diagnosed. Finally, for the global effort toward the prevention of rotavirus disease to be successful, special efforts will be required in India, China, and Indonesia, because one-third of all deaths due to rotavirus disease occur in these countries, and because these countries depend almost entirely on vaccines manufactured domestically.

In the developing world, diarrhea remains the second most common cause of death among children, claiming >2.5 million lives each year and accounting for ~20% of all deaths occurring among children <5 years of age [1]. Efforts to decrease the number of deaths due to diarrhea have targeted interventions to improve water quality and sanitation, promote breast-feeding, and introduce treatment programs based on oral rehydration therapy. Although these efforts have decreased the mortality rate associated with infection due to bacterial and parasitic agents, they have been less effective in reducing rotavirus disease–associated morbidity and mortality [2]. The growing recognition of the importance of rotavirus disease and the high visibility and abortive history of the introduction and withdrawal of RotaShield (Wyeth-Ayerst), the first licensed rotavirus vaccine, have resulted in renewed interest in the prevention of rotavirus disease through the use of vaccine. Furthermore, epidemiological and clinical features of rotavirus diarrhea provide insight into why previous strategies for the control of diarrheal disease have been less successful for the control of rotavirus diarrhea.

RATIONALE FOR ROTAVIRUS VACCINES

Of the >20 different infectious agents known to be associated with the development of diarrhea in children, rotavirus is the most common cause of severe illness.

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Reprints or correspondence: Dr. Roger I. Glass, Mailstop GO4, CDC, 1600 Clifton Rd., Atlanta, GA 30333 (rglass@cdc.gov).

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Rotavirus infections are universal in children during the first few years of life; this suggests that the virus is not primarily transmitted through fecally contaminated food and water and, therefore, that rotavirus infection cannot be prevented through improvements in water and sanitation [3]. Patients with rotavirus infection often present with severe vomiting, a symptom that frequently prompts parents to discontinue oral rehydration therapy, and breast-feeding is not effective in diminishing the severity of disease [4]. Although first infections can lead to disease that ranges from mild gastroenteritis to severe or fatal diarrhea with dehydration, they also can induce immunity against severe disease after reinfection [5]. Consequently, vaccines have been identified as the best strategy to decrease the burden associated with severe and fatal rotavirus diarrhea [6].

During the past 2 decades, many groups reviewing the need for the development of new vaccines, including the World Health Organization (WHO), the Institute of Medicine, and the Global Alliance for Vaccines and Immunization (GAVI), have identified rotavirus vaccines as a priority for development. This decision has been based primarily on the enormous toll of rotavirus disease–associated deaths, which are estimated to number 352,000–592,000 deaths/year (table 1) [7]. Of these deaths, 90% occur in Africa and Asia, >100,000 occur each in India and sub-Saharan Africa, and 35,000 occur in China [8]. Hospital-based surveillance performed in Asia, Africa, and Latin America indicates that 25%–55% of hospitalizations for diarrhea among children <5 years of age are associated with rotavirus infection [9–11] (J.S.B., personal communication). Even in the developed world, vaccines could prevent severe rotavirus disease that, in the United States alone, is associated with ~500,000 physician visits, 60,000 hospitalizations (i.e., 3%–5% of all hospitalizations of children <5 years of age), 20–40 deaths, and annual costs exceeding $1 billion [12–14].

Other factors have also informed the decision to promote the development of rotavirus vaccines. Vaccine development has a solid scientific basis, and natural protection against rotavirus infection was observed in children involved in trials of live oral vaccines. Vaccine developers consider the market for a rotavirus vaccine to be global, because the disease is universal. In addition, within 2–3 years of the introduction of a vaccine, its effect could be measured as a decrease in the number of hospitalizations for diarrhea among children <2 years of age. The introduction and universal application of this vaccine could provide a measurable and visible benefit to the health of a population within 2–3 years.

THE RISE AND FALL OF ROTASHIELD

Immunity to rotavirus infection in infants was first demonstrated by Bishop et al. [15], who observed that newborns who were infected with rotavirus were protected against severe diarrhea after reinfection. Vesikari et al. [16] administered to Finnish infants live oral rotavirus vaccine derived from the bovine Nebraska calf diarrhea virus strain (RIT 4237), which resulted in substantial protection against rotavirus diarrhea that lasted >24 h. This vaccine faltered when the high level of protection repeatedly observed in Finnish infants could not be reproduced among children enrolled in trials in several developing countries [17–19].

Kapikian et al. [20] built on these observations and were able to achieve greater efficacy by combining 4 rotavirus strains into a single vaccine: the tetravalent rhesus rotavirus vaccine

Table 1. Global estimates of and the 10 countries with the greatest number of rotavirus disease–associated deaths per year among children <5 years of age.

Country	No. of rotavirus disease–associated deaths/year	Risk of rotavirus disease–associated death by 5 years of age[a]
India	101,000	1/250
China	35,000	1/540
Nigeria	33,000	1/140
Pakistan	25,000	1/220
Democratic Republic of Congo	20,000	1/130
Ethiopia	20,000	1/150
Bangladesh	13,000	1/320
Afghanistan	12,000	1/90
Indonesia	10,000	1/450
Tanzania	8,000	1/180
Other countries	163,000	1/360
Total	440,000[b]	1/250[c]

[a] Data presented as the no. of deaths/no. of children. Data were calculated by dividing the no. of children in the live birth cohort for each country by the estimated no. of rotavirus disease–associated deaths/year among children <5 years of age. Data are from Parashar et al. [7].
[b] Range, 352,000–592,000 deaths/year.
[c] Range, 1/186 to 1/313.

(i.e., RotaShield). This vaccine combined the rhesus parent strain RRV, which is of serotype G3, with 3 single-gene rhesus-human reassortant strains that contain the genes encoding the 3 most common outer capsid proteins of serotypes G1, G2, and G4, to induce neutralizing antibodies against the 4 most common rotavirus serotypes [20]. This vaccine underwent extensive testing, was manufactured by Wyeth-Ayerst, and, in 1998, became the first rotavirus vaccine to be licensed by the US Food and Drug Administration [21–24]. RotaShield was recommended for the routine immunization of children, with 3 oral doses administered at 2, 4, and 6 months of age [25].

Uptake of the vaccine was rapid, and, over the next 9 months, ~600,000 infants (~17% of the national birth cohort) received >1.2 million doses, despite the suggested retail price of $38/dose. In July 1999, a cluster of 15 cases of intussusception was recognized among children within 2 weeks after they received a first dose of the vaccine [26]. Intense epidemiological investigation of this rare adverse event led to confirmation of a causal association with the vaccine [27, 28]. The risk of vaccine-associated intussusception was estimated to be 1 case/11,000 vaccine recipients [29], although the range of estimates varied >100-fold, from 1 case of intussusception/2500 vaccine recipients (on the basis of early and incomplete data) to 1 case/9500 vaccine recipients (on the basis of the case-control study), to 1 case/66,000–302,000 vaccine recipients [26, 30] (on the basis of ecological studies in which the certainty of case ascertainment was unknown). This association led to the withdrawal of the vaccine in the United States and precluded its introduction in the developing world, where it is estimated that 1 child in 250 dies of rotavirus disease. A consensus conference, hosted by WHO and involving pediatricians, ethicists, health care professionals, and pharmaceutical representatives, concluded that the experience with RotaShield in the United States was sufficiently damaging that application of this vaccine elsewhere would be unlikely [6, 31].

The exact pathogenic mechanism by which RotaShield might cause intussusception was never determined. It was subsequently determined that the primary risk factor for intussusception was older age (i.e., ⩾90 days) at the time of initial vaccination: 80% of the complications occurred among the 50% of children who were ⩾90 days of age at the time of vaccination with the first dose, whereas only 20% of these severe adverse events occurred among the 50% of children who were <90 days of age [32]. Of note, natural intussusception is uncommon in children during the first few months of life, so whatever mechanisms reduce the susceptibility of an infant to this natural disease also appeared to have reduced the susceptibility to intussusception induced by RotaShield. In retrospect, had the first dose of vaccine been administered only to children <90 days of age, the risk of intussusception could have been substantially reduced to approximately ⩽1 case/30,000 vaccine recipients.

THE VACCINE HORIZON

The withdrawal of RotaShield led to a reassessment of the future of live oral rotavirus vaccines. At least 7 different live oral candidate vaccines were in development at the time, and each manufacturer had to reassess whether its vaccine might cause intussusception (table 2). Despite the tumult surrounding the withdrawal of RotaShield, several positive outcomes emerged that have given new life to the next generation of live oral vaccines. First, development accelerated because of competition. Both Merck and GlaxoSmithKline (GSK) have rotavirus vaccines that have completed clinical development, with >60,000 children enrolled in each trial to assess the risk that the vaccines might cause a low incidence of intussusception. A Chinese manufacturer, the Lanzhou Institute of Biological Products, produces a vaccine based on a lamb strain that is licensed in China [33]. Manufacturers in India (Bharat Biotech) and Indonesia (Bio Farma) have naturally occurring neonatal strains that are being considered as candidate vaccines [33].

The 2 vaccines from the multinational vaccine manufacturers are based on different principles and will first be targeted to different markets: the GSK vaccine will be targeted for use in Latin America, and the Merck vaccine will be targeted for use in the United States. The GSK vaccine has been licensed for use in Mexico and the Dominican Republic, and the Merck vaccine could be licensed within 1–3 years. Results from the trials are not yet available, but preliminary data suggest that both vaccines will be safe and effective.

The GSK vaccine, Rotarix, is derived from a single human rotavirus strain (89-12; P1A[8],G1) that was attenuated by multiple passages in cell culture. Because natural rotavirus infection protects children against severe disease on reinfection, the basis for cross-protection between strains has been established, and a single vaccine strain could mimic this protection. Trials in which 2 oral doses were administered to >6000 children in Brazil, Venezuela, and Mexico demonstrated 79% efficacy against severe disease leading to a clinic or physician visit [34]. Large trials of the safety of the vaccine have been completed in Latin America, which will be the first target for introduction.

The Merck vaccine, RotaTeq, is composed of 5 rotavirus strains, each of which is a single-gene reassortant based on a parent bovine strain (WC3) that contains an outer capsid gene from a human strain that induces immunity to the most common antigenic types of rotavirus in circulation (G1–G4 and P1A) (table 2). Animal strains of rotavirus do not provide the same level of cross-protection against other human serotypes; therefore, to improve the efficacy of animal strains, reassortant strains that bear the capsid genes from the other common human strains are required. The safety of this vaccine has been tested in trials involving >60,000 children in the United States and Finland, but the results have not yet been published.

The National Institutes of Health has 2 candidate vaccines.

Table 2. Status of rotavirus vaccines in development.

Vaccine	Manufacturer (location)	Rotavirus strains (genotype)	Status of vaccine	Efficacy
RotaTeq	Merck (United States)	Pentavalent human-bovine reassortants WC3 × WI79 (P7[5],G1), WC3 × SC2 (P7[5],G2), WC3 × W178 (P7[5],G3), WC3 × BrB (P7[5],G4), and WC3 × WI79 (P1A[8],G1)	Phase 3 trial involving >60,000 children	Pending
Rotarix	GlaxoSmithKline (Belgium)	Monovalent, attenuated human strain 89-12 (P[8],G1)	Phase 3 trial involving >60,000 children	90% in Venezuela, Brazil, and Mexico
LLR	Lanzhou Institute of Biological Products (China)	LLR strain (P[12],G10)	Licensed in China in 2000	Not evaluated in a randomized controlled trial
RV3	University of Melbourne (Australia) and Bio Farma (Indonesia)	Monovalent neonatal human strain (P2A[6],G3)	Phase 2 trial	ND
UK reassortant vaccine	NIH (United States)	Tetravalent human-bovine reassortant UK × Wa (P7[5],G1), UK × DS1 (P7[5],G2), UK × P (P7[5],G3), and UK × ST3 (P7[5],G4)	Phase 2 trial	Pending
Indian neonatal vaccines	Bharat Biotech (India)	Neonatal strains 116E (P[11],G9) and I321 (P[11],G10)	Phase 1 trial	ND
Rhesus tetravalent	BIOVIRx (United States)	Tetravalent human-rhesus reassortants RRV × D (P5[3],G1), RRV × DS1 (P5[3],G2), RRV (P5[3],G3), and RRV × ST3 (P5[3],G4)	Licensed by the US FDA but currently not manufactured	>90% in the United States and Finland and 70% in Venezuela

NOTE. FDA, Food and Drug Administration; LLR, Lanzhou lamb rotavirus; ND, not determined; NIH, National Institutes of Health; WC3, bovine rotavirus strain.

One vaccine is a multivalent vaccine made from bovine-human (UK) reassortant strains that has been proven to be effective in clinical trials [35], and the other is a tetravalent rhesus rotavirus vaccine that has been relicensed to a small biotechnology firm (BIOVIRx), which is considering further manufacture of the vaccine.

UNANSWERED QUESTIONS: CHALLENGES REGARDING THE NEXT GENERATION OF ROTAVIRUS VACCINES

Although rotavirus vaccines are among the new vaccines closest to global introduction, many challenges remain before they can become part of the universal program for childhood immunization.

1. *Will live oral rotavirus vaccines work well for children in the developing world?* A major scientific concern for rotavirus vaccines, as well as all live oral vaccines, is to assess whether they will work as well for children in the poor developing countries of Africa or Asia as they do for children in the United States, Europe, or Latin America. To date, no live oral rotavirus vaccine has had efficacy demonstrated in Africa or in a poor country in Asia. RIT 4237, the first rotavirus vaccine that was highly effective in Finnish children, failed to protect children in Rwanda and The Gambia, as well as children on a Navajo reservation in the southwestern United States, regions where early infection with rotavirus occurred [17–19, 36]. This concern about the efficacy of live oral rotavirus vaccines is similar to the experience with both live oral poliovirus and cholera vaccines that proved to be less immunogenic and protective in many parts of the developing world than in most of North American and Europe [37, 38]. For RotaShield, the WHO requested that the efficacy of RotaShield be confirmed in at least 1 trial involving infants in poor areas of Africa and Asia before it would consider recommending the vaccine for widespread use [39]. For the Merck and GSK vaccines, such confirmatory tests in developing counties will be critical before the vaccines can be recommended for global use.

2. *How safe will they be?* The US Food and Drug Administration's requirement that the next generation of vaccines be safer than the first generation of vaccines represents a difficult hurdle for multinational vaccine manufacturers. Each company is engaged in safety trials involving 30,000 vaccine recipients and 30,000 placebo recipients, a sample size chosen on the basis of preliminary estimates of the earliest risk of intussusception resulting from vaccination with RotaShield. New data have reduced the risk of intussusception from 1 case/4500 vaccine recipients to 1 case/11,000 vaccine recipients, and the recent observation that 80% of cases of intussusception occurred in the 50% of children who were $\geqslant$90 days of age at the time of vaccination has even further reduced the risk among younger children (i.e., children <90 days of age). Thus, even when licensed, these vaccines will have a safety profile that will not yet be proven to be safer than that of RotaShield. Only by performing postlicensure surveillance after hundreds of thousands of children have been vaccinated will we know whether the new vaccines are associated with a lower risk or any risk of intussusception. Furthermore, for developing countries where rotavirus infection is often fatal, the benefits of the vaccine in the prevention of rotavirus disease–associated deaths (estimated to be 1 case/250 vaccine recipients) could well overshadow this level of risk of intussusception seen with the use of RotaShield.

3. *What will they cost, and how can we pay for them?* The next generation of rotavirus vaccines can have a beneficial effect only if funding mechanisms are in place to provide them to the most needy children in the world. The vaccines themselves are prepared using traditional tissue culture technology, and they should, in theory, be inexpensive to produce. At the same time, the development costs for large-scale trials by the multinational vaccine manufacturers are enormous, and, thus, the pricing mechanisms and levels of tiered prices will be critical. The Vaccine Fund and the GAVI have committed to purchase vaccines for the 74 poorest countries of the world. The incentive exists in the future to include rotavirus vaccines on the list of approved vaccines.

4. *Who will provide the bulk of the vaccine supply?* Although the multinational vaccine manufacturers are best recognized for their new and innovative vaccines, in fact, most of the vaccines currently purchased by the United Nations Children's Fund for national programs come not from large multinational vaccine manufacturers but, rather, from emerging manufacturers. Furthermore, 3 countries where mortality associated with rotavirus disease is high—that is, India, China, and Indonesia—depend almost exclusively on domestic manufacturers for their vaccines. Multinational vaccine manufacturers have little or no penetration into the markets in the public sector of these countries, and this low-price, high-volume model is not part of their business plan for new vaccines. Consequently, special efforts will be required to encourage emerging manufacturers to accelerate their own efforts toward the domestic manufacture of vaccine.

5. *Will countries be interested in a new rotavirus vaccine?* Despite global estimates of the enormous burden of rotavirus diarrhea, few policy makers or pediatricians have adequate data to assess the burden of rotavirus disease in their own country or to make a rational policy decision regarding the value of a new rotavirus vaccine. Despite the availability of simple, sensitive, and inexpensive test kits, a diagnosis of rotavirus disease is rarely sought, and it would be hard to introduce a new vaccine against a disease whose local importance is unrecognized. To address this problem and to create a cadre of knowledgeable advocates, surveillance networks are being set up in different

regions to develop a global database, by use of a generic protocol prepared by the WHO [40]. Networks in Africa, Asia (including India and China), and Latin America are already in place, and rotavirus is detected in 30%–55% of children hospitalized with diarrhea (J.S.B., personal communication). Nonetheless, it will take time for these activities to become established and produce sufficient local data so that countries can consider the need for a rotavirus vaccine when they become available.

6. Will parents accept a vaccine for only 1 cause of childhood diarrhea? A nagging question remains as to whether mothers might feel cheated or misled if their child received a rotavirus vaccine but still developed diarrhea, albeit of a different etiology. For example, a mother in Bangladesh would hardly recognize the effect of the vaccine because her child might experience 20–30 episodes of diarrhea during the first 5 years of life, only 1 of which is due to rotavirus. At the same time, the pediatricians, public health care staff, and hospital administrators should witness a sharp decrease in the treatment of children with severe diarrhea. As the next generation of vaccines is introduced, it will be important to craft the appropriate educational messages so that mothers are not disappointed. Of note, other childhood vaccines against respiratory syndromes (e.g., influenza, pneumococcal disease, and pertussis) and meningitis (due to *Haemophilus influenzae* type B and *Streptococcus pneumoniae*) also only provide protection against a subset of pathogens, and, for parents, such problems of perception have not been an issue.

THE NEXT STEPS

Rotavirus vaccines have been granted a high priority on the global agenda for the development and introduction of a new vaccine. GAVI has identified the development and introduction of rotavirus vaccines as 1 of 3 key priorities requiring increased attention. This priority will be promoted by the Rotavirus Vaccine Program, a $30-million-dollar effort funded for 3 years to achieve these goals. This program will accelerate the introduction of vaccines nearing licensure, with the specific goal of assessing whether these vaccines are safe and efficacious for children in the poorest countries, where support for the purchase of vaccine might be facilitated through the Vaccine Fund. Additional efforts will be needed to encourage work on vaccines in earlier stages of development, including those being prepared by emerging manufacturers in the developing world—in particular, in India, China, and Indonesia. A consortium of 4 organizations funded by the Bill and Melinda Gates Foundation and supported through the Program for Appropriate Technology in Health is working with an Indian manufacturer to develop the Indian neonatal vaccine as a first vaccine for India [41]. The goal of these efforts will ultimately be to demonstrate that the next generation of rotavirus vaccines can be safe, effective, affordable, and available in a supply adequate to immunize up to 60% of the world's children within a decade. This will require a massive effort, but quick, early, and visible reductions in the number of hospitalizations should help to accelerate rapid introduction of vaccine and encourage greater investment, increased supply, and lower cost. The challenge is considerable, and the effect should be measurable quickly, within 2–3 years.

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